REMARKS

Claims 53-65 are pending in the application. Claims 53-56 have been amended. Please cancel claims 59-65 without prejudice to prosecution in further applications. Please add new claims 66-67. Accordingly, upon entry of the amendments presented herein, claims 53-67 and 66-68 will remain pending in the application.

Support for the amendments to the specification and the claims can be found throughout the specification and the claims as originally filed. Specifically, support for the amendments to claim 53 may be found at least, for example, at page 44, lines 12-15; page 14, lines 4-13; page 15, line 33 through page 21, line 2 of the specification. Specifically, support for the amendments to claims 54-56 may be found at, at least, for example, page 22, lines 18-32; and page 67, lines 1-17 of the specification. Support for new claim 66 may be found at least, for example, at page 2, lines 30-33. Support for new claim 67 may be found at least, for example, at page 3, line 7.

No new matter has been added. Any amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was performed solely in the interest of expediting prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objection to the Specification

At paragraph 3 of the pending Office Action, the Examiner objects to the disclosure because it recites "Brief Description of the Figures" instead of "Brief Description of the Drawings," as is required by M.P.E.P. § 608.01(f).

Applicants have amended the specification to recite the phrase "Brief Description of the Drawings," thereby rendering this objection moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

Sequence Requirements

At paragraph 4 of the pending Office Action, the Examiner states that:

> Applicant provided a sequence listing on 1/25/01 but did not direct its entry into the specification. There was no amendment stating that the prior sequence listing be cancelled and replaced with the sequence listing dated 1/2/501 [*sic*]. A further sequence listing was provided on 11/18/04. Again there was no amendment stating that the prior sequence listing be cancelled and replaced with the sequence listing dated 11/18/04. The record is not clear as to which sequence listings should be cancelled. Appropriate correction is required.

In response, Applicants respectfully note that a Sequence Listing was originally filed with the application on June 30, 2000. A substitute Sequence Listing was subsequently filed on January 22, 2001[1]. In response to the Office Action dated May 18, 2005, an additional substitute Sequence Listing was filed on November 18, 2004. Finally, in response to the Office Communication dated March 8, 2005, a paper substitute Sequence Listing was filed on April 7, 2005, along with a diskette containing the substitute Sequence Listing and the appropriate statement under 37 C.F.R. 1.825(a) and 1.825(b). Accordingly, Applicants respectfully request that the Sequence Listings filed on June 30, 2000, January 22, 2001 and November 18, 2004 be replaced with the Sequence Listing filed on April 7, 2005. Furthermore, Applicants respectfully request that the Sequence Listing filed on April 7, 2005 be entered into the specification.

Rejection of Claims 53-58 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 53-58 under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner is of the opinion that claim 53 is "indefinite because it is not clear what activity of the MEKK protein is regulated in the cell such that apoptosis of the cell is regulated" and suggests that "a specific activity be disclosed" in order to overcome this rejection. Furthermore, the Examiner asserts that "it is not clear if 'directly regulates"

[1] The Examiner indicates that a Sequence Listing was filed on 1/25/01 and/or 1/2/501. As a Sequence Listing was not submitted on January 25, 2001, Applicant assumes that the Examiner is referring to the Sequence Listing filed on January 22, 2001.

means the agent must bind to the MEKK to exert its effect or if regulation is by some other means."

While in no way acquiescing to the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have amended claim 53 to recite a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly interacts with and modulates the activity of an MEKK 1 polypeptide set forth as SEQ ID NO:2 or 4, such that apoptosis of the cell is regulated, wherein the activity of the MEKK 1 polypeptide is selected from the group consisting of: being phosphorylated, phosphorylating a MEKK substrate, regulating the activity of a MEKK substrate, controlling the phosphorylation of a MEKK signal transduction protein, and regulating the activity of a MEKK signal transduction protein. Accordingly, the foregoing rejection of claim 53, and claims depending therefrom, is moot.

Furthermore, claims 54-56 are rejected as being indefinite because, according to the Examiner, it is unclear which fragments of MEKK contain the critical structural feature of the invention to be classified as the kinase domain, the regulatory domain, and the kinase catalytic domain of MEKK protein.

Claims 54-56, as amended, specify clear and definite structural features of the claimed domains. Accordingly, the foregoing rejection is moot.

Finally, claims 57 and 58 are rejected "for depending on an indefinite base (or intermediate) claim." In light of the amendment to claim 53, Applicants respectfully submit that this rejection is moot.

In view of all of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the foregoing rejections.

Rejection of Claims 53-58 Under 35 U.S.C. § 112, First Paragraph - Enablement

The Examiner has rejected claims 53-58 under 35 U.S.C. § 112, First Paragraph, because, according to the Examiner:

> the specification, while being enabling for a method for regulating cell apoptosis of a cell containing an MEKK-1 polypeptide set forth in SEQ ID NO: 2 or MEKK1.2 polypeptide set forth in SEQ ID NO:4 comprising contacting the cell with an agent that binds to MEKK protein of SEQ ID NO:2 or 4 or the truncated MEKK disclosed in Example 15, wherein said agent regulates the ability of said MEKK to be phosphorylated or to phosphorylate a substrate such as MAP kinase or other substrate disclosed in the Examples such that apoptosis is regulated, does not reasonably provide enablement for other MEKKs or agents that stimulate MEKK activity.

While in no way acquiescing to the Examiner's rejection, and solely in the interest of expediting prosecution, Applicants have amended claim 53, as discussed above, to recite a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly interacts with and modulates the activity of an MEKK 1 polypeptide set forth as SEQ ID NO:2 or 4, such that apoptosis of the cell is regulated, wherein the activity of the MEKK 1 polypeptide is selected from the group consisting of: being phosphorylated by MEKK, phosphorylating a MEKK substrate, regulating the activity of a MEKK substrate, controlling the phosphorylation of a MEKK signal transduction protein, and regulating the activity of a MEKK signal transduction protein.

Accordingly, contrary to the Examiner's assertion, the pending claims are not drawn to "other MEKKs." Instead the pending claims are drawn only to MEKK 1, an embodiment which, as acknowledged by the Examiner, is enabled by the specification. Moreover, Applicants respectfully submit that agents that stimulate MEKK activity are indeed enabled by the present specification. For example, at page 28, lines 5-32 of the present specification, Applicants disclose various peptide and non-peptide agents which can be used in the claimed methods, as well as methods for generating the agents. Based on these teachings, as well as the level of knowledge in the art, one of ordinary skill in the art would be able to generate and identify the agents utilized in the claimed invention.

Accordingly, amended claim 53, and claims depending therefrom, are drawn to methods which are fully enabled and supported by the specification. As such, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Furthermore, the Examiner has rejected claims 53-58 under 35 U.S.C. § 112, First Paragraph, because, the Examiner is of the opinion that

> while the skilled artisan, in light of the specification, would be able to use the MEKK1 disclosed in SEQ ID NO:2 and 4, or the polypeptide disclosed in Example 15, to regulate the MEKK protein to be phosphorylated or phosphorylate a substrate to regulate cell apoptosis, there is no disclosure in the specification or prior art that variants encompassed by only the name MEKK (name provides no structure and function association), variants with 85% identity with the regulatory domain of SEQ ID NO:2 or 4, variants with 85% identity with catalytic domain of SEQ ID NO: 2 or 4, or proteins that can be used to regulate activity of a MEKK protein in a cell such that apoptosis is regulated. Also, it must be noted that no agents are disclosed that increase apoptosis of cells by increasing MEKK activity. Therefore applicants are not enabled for methods involving the use of agents to increase apoptosis by regulating MEKK activity.

Applicants traverse the foregoing rejection and respectfully submit that based on the teachings in Applicants' specification, as well as the knowledge generally available at the time the application was filed, a skilled artisan would be able to make and use the claimed methods using only routine experimentation. As discussed above, the pending claims are not drawn to "a MEKK protein," but are instead drawn only to MEKK 1, an embodiment which, as acknowledged by the Examiner, is enabled by the specification. Moreover, Applicants teach various peptide and non-peptide agents which can be used in the claimed methods. As such, the specification does enable "the use of agents." Finally, Applicants respectfully submit that since the claims no longer recite "variants with 85% identity," this rejection is now moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections.

Rejection of Claims 53 and 54 Under 35 U.S.C. § 102(b)

Claims 53 and 54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dubroff (U.S. Patent No. 5,080,647). Specifically, the Examiner is of the opinion that

> Dubroff discloses a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly regulates the that [sic] apoptosis of the cell. Dubroff discloses compositions and methods for their use in killing undifferentiated epithelial cells (see abstract, claims and columns 1-6). The compositions and method of Dubroff will inherently modulate the activity of an MEKK 1 polypeptide set forth as SEO [sic] ID NO:2 or 4 (phosphorylation or cell death for example) because the compounds disclosed will cause cell apoptosis and degradation or denaturation of the proteins contained within. Therefore the disclosure of Dubroff meets the limitations of claims 53 and 54, absent evidence to the contrary.

Applicants respectfully traverse the foregoing rejection. For a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Claim 53, as amended, and claims depending therefrom, are drawn to a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly interacts with and modulates the activity of an MEKK 1 polypeptide set forth as SEQ ID NO:2 or 4, such that apoptosis of the cell is regulated, wherein the activity of the MEKK 1 polypeptide is selected from the group consisting of: being phosphorylated, phosphorylating a MEKK substrate, regulating the activity of a MEKK substrate, controlling the phosphorylation of a MEKK signal transduction protein, and regulating the activity of a MEKK signal transduction protein.

Contrary to the Examiner's assertion Dubroff, do not teach *each* and *every* element of the pending claims. Specifically, Dubroff teach the use of cell-killing substances (*i.e.*, hypotonic solutions such as distilled water or water having a salinity less than 0.9%) which "destroy...undifferentiated epithelial cells by osmolysis or by destructive pH alteration" (see

column 4, line 13-47). Dubroff do *not* teach or even suggest agents that would directly interact with and/or modulate the activity of MEKK 1.

Moreover, Dubroff do *not* teach or even suggest a method for regulating apoptosis of a cell. Apoptosis is programmed cell death, *i.e.*, it is a regulated process of deliberate life relinquishment by an unwanted cell in a multicellular organism. As taught by Applicants at page 19, line 37 through page 20, line 5, "apoptosis refers to the form of cell death that comprises: progressive contraction of cell volume with the preservation of the integrity of cytoplasmic organelles; condensation of chromatin, as viewed by light or electron microscopy; and DNA cleavage, as electrophoresis or labeling of DNA fragments using terminal deoxytransferase (TDT)." In sharp contrast to the ordered process of apoptosis that is regulated by the claimed methods, Dubroff teach a form of cell killing initiated by serious physical and/or chemical insult to the cells (*e.g.*, necrosis) that results from acute cellular injury (*i.e.*, cell swelling and lysis). Accordingly, Dubroff fail to teach or suggest each and every element of amended claim 53 and claims depending therefrom. As such, Applicants respectfully request that the foregoing section 102(b) rejection be reconsidered and withdrawn.

Rejection of Claims 53, 54, 57 and 58 Under 35 U.S.C. § 102(e)

Claims 53, 54, 57 and 58 are rejected under 35 U.S.C. § 102(e) as being anticipated by Naficy (U.S. Patent No.: 5,419,759). According to the Examiner

> Naficy discloses a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly regulates the that [*sic*] apoptosis of the cell. Naficy discloses compositions and methods for their use in killing HIV infected cells (see abstract, columns 1-14). In column 9 Naficy discloses killing H-9 lymphocytes with the use of ether. The compositions and method of Naficy will inherently modulate the activity of an MEKK 1 polypeptide set forth as SEO [*sic*] ID NO:2 or 4 (phosphorylation or cell death for example) because the compounds disclosed will cause cell apoptosis and degradation or denaturation of the proteins contained within. The method of Naficy is used to kill T cells, which are involved in an inflammatory response. Therefore the disclosure of Naficy meets the limitations of claims 53-54 and 57-58, absent evidence to the contrary.

Applicants respectfully traverse the foregoing rejection. For a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). As discussed above, claim 53, as amended, and claims depending therefrom, are drawn to a method for regulating apoptosis of a cell comprising contacting the cell with an agent that directly interacts with and modulates the activity of an MEKK 1 polypeptide set forth as SEQ ID NO:2 or 4, such that apoptosis of the cell is regulated, wherein the activity of the MEKK 1 polypeptide is selected from the group consisting of: being phosphorylated, phosphorylating a MEKK substrate, regulating the activity of a MEKK substrate, controlling the phosphorylation of a MEKK signal transduction protein, and regulating the activity of a MEKK signal transduction protein.

Contrary to the Examiner's assertion Naficy do not teach *each* and *every* element of the pending claims. Specifically, Naficy teach an extracorporeal method for killing infected H-9 lymphocytes by incubating the infected lymphocytes with an organic agent, such as diethyl ether (see abstract; column 9, line 18-47). Naficy do *not* teach or even suggest that agents that would directly interact with and/or modulate the activity of MEKK 1.

Moreover, Naficy do *not* teach or even suggest a method for regulating apoptosis of a cell. As set forth above, apoptosis is programmed and controlled cell death, *i.e.*, it is a regulated process of deliberate life relinquishment by an unwanted cell in a multicellular organism. In sharp contrast to the ordered process of apoptosis that is regulated by the claimed methods, Naficy teach a form of cell killing initiated by serious physical and/or chemical insult to the cells (*e.g.*, necrosis) that results from acute cellular injury (*i.e.*, cell swelling and lysis). Accordingly, Naficy fail to teach or suggest each and every element of amended claim 53 and claims depending therefrom. Accordingly, Applicants respectfully request that the foregoing section 102(b) rejection be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney could be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: May 22, 2006

Respectfully submitted,

By _____
Debra J. Milasincic
Registration No.: 46,931
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicants